Amendments to the Specification:

Please replace paragraph 1 with the following amended paragraph:

CROSS-REFERENCES TO RELATED APPLICATIONS

This application is a continuation of U.S. Application No. 10/021,168, filed on December 11, 2002, which is a continuation of U.S. Application No. 08/970,447, filed on November 14, 1997, which is a continuation of U.S. Application No. 08/666,264, filed on June 20, 1996, now U.S. Patent No. 5,693,676, which is a continuation of U.S. Application No. 08/371,088, filed on January 10, 1995, now abandoned, which is a continuation-in-part of U.S. Application No. 08/250,555, filed on May 27, 1994, now U.S. Patent No. 5,504,117. The disclosures of each of which are herein incorporated by reference in their entireties for all purposes.

Please add the following new paragraphs after the first sentence of the Detailed Description on page 9:

The role of nitric oxide in relaxation of the internal anal sphincter (IAS) in response to the rectoanal reflex has been studied in the opossum by others (*see,* Rattan S., Sarkar A., Chakder S., *Gastroenterology*, (1992 Jul), 103(1):43-50). They monitored resting pressures in the IAS using low-compliance continuously perfused catheters and reported the following.

L-NG-nitro-arginine (L-NNA), a NO-synthase inhibitor, caused significant dose-dependent suppression of the decrease in resting pressures in the IAS in response to the reflex mimicked by the rectal balloon distention. IAS relaxation in response not only to rectoanal reflex but also to other neural stimuli such as sacral nerve stimulation, local intramural stimulation, and the nicotinic ganglionic stimulant 1,1-dimethyl-4-phenylpiperazinium was also blocked by an NO-synthase inhibitor. The suppression of the neurally mediated IAS relaxation by L-NNA was stereoselective; D-NNA had no effect on the relaxation. The suppression of the rectoanal reflex-induced IAS relaxation by L-NNA was completely reversed by NO precursor L-arginine

stereoselectively as D-arginine failed to reverse the suppressed IAS relaxation. The decrease in the resting pressure of the IAS caused by sodium nitroprusside was modified neither by the neurotoxin tetrodotoxin nor by L-NNA. Furthermore, the inhibitor of NO synthase did not modify the decrease in the resting pressure of the IAS by the direct-acting beta-adrenoceptor agonist isoproterenol. It was concluded that NO or a NO-like substance is an important mediator of IAS relaxation in response to noradrenergic, noncholinergic nerve stimulation.

Another study by others on the release of nitric oxide by activation of nonadrenergic noncholinergic neurons of internal anal sphincter has also been reported (*see*, Chakder S., Rattan S., *Am J. Physiol*, (1993 Jan), 264(1 Pt 1):G7-12.). This study investigated the direct release of nitric oxide (NO) in response to the stimulation of nonadrenergic noncholinergic (NANC) nerves. Isolated smooth muscle strips of the opossum (Didelphis virginiana) internal anal sphincter (IAS) were used. This study reported the following:

Electrical field stimulation (EFS) of these strips using the appropriate parameters was reported to cause a frequency-dependent fall in the resting tone of the IAS. The chemiluminescence method was used in the study to measure the release of NO. The stimulation of NANC neurons by the nicotinic stimulant 1,1-dimethyl-4-phenylpiperazinium (DMPP) and EFS caused IAS relaxation with an accompanying release of NO. The study found pretreatment of the smooth muscles with the neurotoxin tetrodotoxin and the NO-synthase inhibitor NG-nitro-L-arginine (L-NNA) abolished the release of NO and the fall in the resting tension of IAS in response to lower frequencies of EFS and DMPP. Addition of the NO precursor L-arginine reversed to control levels of the loss of the release of NO and the IAS relaxation in the presence of L-NNA. Again, the effect of L-NNA and L-arginine on NO release and IAS relaxation was stereoselective. D-NNA and D-arginine had no significant effect. The release of NO from IAS smooth muscle strips caused by vasoactive intestinal polypeptide was also abolished by L-NNA. However, both isoproterenol and atrial natriuretic factor caused IAS relaxation without any increase in NO release. These investigations show that NO is directly released in response to the stimulation of gut NANC inhibitory neurons.

An additional study of nerve mediated relaxation of the human internal anal sphincter investigated the role of nitric oxide. *See*, O'Kelly T., Brading A., Mortensen N., *Gut*, (1993 May) 34(5):689-93. This reference concerns whether nitric oxide (NO) is the non-adrenergic, non-cholinergic neurotransmitter which is released by enteric inhibitory nerves to mediate relaxation of the human internal anal sphincter. Isolated muscle strips were mounted in a superfusion organ bath so as to record their isometric tension. This study reported the following: An exogenous donor of NO, sodium nitroprusside, relaxed the strips in a dose dependent manner. In the presence of atropine and guanethidine, transmural field stimulation produced relaxations. These relaxations were sensitive to tetrodotoxin. These relaxations were also inhibited in a concentration dependent and stereospecific manner by antagonists of NO synthase; completely by L-nitroarginine and partially by L-N-monomethyl arginine. These inhibitory effects were reversed by L-arginine. D-arginine did not reverse them. The relaxations were abolished by the nitric oxide scavenger, oxyhaemoglobin, but not methaemoglobin. The O'Kelly, et al. findings strongly indicated that NO is, or is very closely associated with, the non-adrenergic, non-cholinergic neurotransmitter which mediates the neurogenic relaxation of the human internal anal sphincter.